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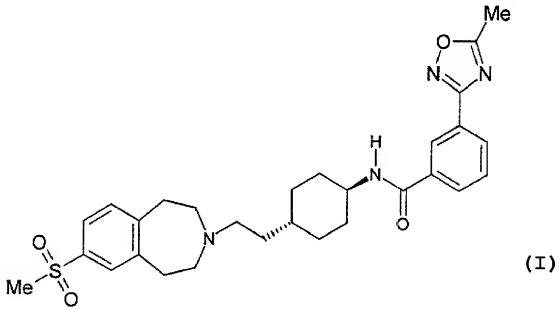
(54) Titre : COMPOSE NOUVEAU
(54) Title: NOVEL COMPOUND



(I)

(57) Abrégé/Abstract:
The present invention provides a hydrochloride (HCl) salt of the compound of formula (I): (see formula I) especially the monohydrochloride salt thereof; pharmaceutical preparations including such salts; and use of the salts in the treatment and prophylaxis of disorders including psychotic disorders, substance abuse or addiction, dyskinetic disorders, depression, anxiety, cognitive impairment, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders, or gastric motility disorders.

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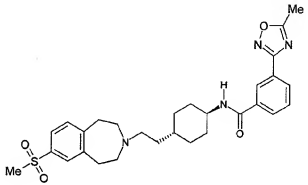
Abstract

The present invention provides a hydrochloride (HCl) salt of the compound of formula (I) :



Formula (I)

especially the monohydrochloride salt thereof; pharmaceutical preparations including such salts; and use of the salts in the treatment and prophylaxis of disorders including psychotic disorders, substance abuse or addiction, dyskinetic disorders, depression, anxiety, cognitive impairment, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders, or gastric motility disorders.

P32781

NOVEL COMPOUND

The present invention relates to the hydrochloride salt of a tetrahydrobenzazepine compound whose structure is set out as formula (I) below, and in particular to the monohydrochloride salt thereof. The invention further relates to processes for preparation of the hydrochloride salt, pharmaceutical compositions containing the hydrochloride salt and the use thereof in the treatment or prophylaxis of conditions including psychosis, substance addiction, and substance abuse.

US Patent No. 5,294,621 describes certain tetrahydropyridine derivatives as antiarrhythmic agents. EPA 431,580 describes cyclohexyl-containing compounds as dopaminergic agents useful as antipsychotics, antihypertensives and also of use in the treatment of hyperprolactinaemia-related conditions and several central nervous system disorders. WO 95/10513 describes benzothiophene derivatives and related compounds as estrogen agonists.

WO 97/43262, WO 98/06699, WO 98/49145, WO 98/50363, WO 98/50364, WO 98/51671, WO 99/59974, WO 99/64412 and WO 00/24717 describe tetrahydroisoquinoline derivatives as having affinity for the dopamine D_3 receptor.

WO 00/21951 describes a class of tetrahydrobenzazepine derivatives which have affinity for dopamine receptors, in particular the D_3 receptor, and use of these derivatives as antipsychotic agents.

The present invention seeks to provide further products with advantageous properties for use in the treatment and/or prophylaxis of psychotic conditions including schizophrenia; and substance abuse and addiction.

According to one aspect of the present invention, there is provided a hydrochloride salt of the compound of formula (I)

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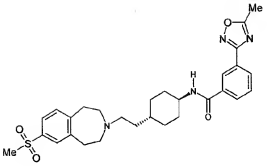


Formula (I)

Preferably, said salt is a monohydrochloride salt of the compound of formula (I).

As will be appreciated, the compound of formula (I) exists in the form of the *trans*-isomer with respect to the configuration at the cyclohexyl ring. Because of the axis of symmetry about the cyclohexyl ring, there are not two diasteromeric forms: the form with the left-hand bond to the ring drawn upwardly from the paper and with the right-hand C-N bond to the ring drawn downwardly into the paper is identical to the form shown in Formula (I).

Said salt may be in hydrated or anhydrous form, the anhydrate being especially preferred, owing to its good processability. Advantageously, said salt may be in anhydrate form, and may preferably be substantially free from hydrated forms of the salt.

Suitably, said salt may be in isolated, advantageously in purified, form. Thus, when in isolated form said salt can be free or substantially free from organic and/or aqueous solvents, including body fluid solvents, such as water, or organic solvents such as dichloromethane.

Preferably, said salt is free or substantially free from the free base of formula (I), and/or from other salts thereof.

The present inventors have found that the hydrochloride salt of the present invention enjoys a range of advantageous properties and is especially suited for use in the treatment of psychosis, addiction and substance abuse, including cocaine, heroin, nicotine and alcohol addiction and abuse. Affinity and functional studies indicate that said salt binds strongly to the D3 dopamine receptor, and has an antagonistic effect on D3 receptor activity. Consequently, the salt is expected to be useful in the treatment of conditions for which modulation, typically

antagonism, of the D3 dopamine receptor is beneficial. Moreover, the salt shows a high degree of selectivity for the D3 receptor over the D2 dopamine receptor, and over a number of other pharmaceutically relevant receptors. This selectivity is expected to lead to a reduction in extrapyramidal side-effects, typically associated with the use of many neuroleptic agents, when the salt is used for treatment of a patient.

Tests have shown the HCl salt of the present invention to display good (75%) oral bioavailability in dog, indicating its suitability for oral administration to patients.

Furthermore, the physical properties of said hydrochloride salt facilitate easy and efficient formulation of the salt and administration thereof for therapeutic purposes. The salt is readily obtainable in the anhydrate (anhydrous) form which is easy to process. The hydrochloride salt is highly soluble in water, having an aqueous solubility of around 3-4 mg/ml after 24 hours. This is greater than the solubility of the corresponding free base form by a factor of about 10^3. The hydrochloride salt, in particular the anhydrate form thereof, enjoys good stability, 99.9% of the salt remaining undecomposed after 1 month both at 50°C/normal ambient humidity, and at 40°C/75% humidity. The HCl salt of the compound of formula (I) furthermore demonstrates good photostability in comparison with the free base form, which undergoes a visible change in colour from white to yellow on exposure to light.

According to another aspect of the present invention, there is provided a method for preparing a hydrochloride salt of the compound of formula (I), comprising the steps of: dissolving or suspending in a solvent a compound of formula (I) in free base form; and mixing said free base with hydrogen chloride to allow formation of said salt.

Optionally, the method comprises the earlier step of preparing or obtaining a compound of formula (I) in free base form. Preferably, the method starts with/from the free base.

Preferably, said method further comprises the step of causing or allowing said salt to crystallise and isolating said crystallised salt.

Suitably, said solvent may be an organic solvent. Said solvent may comprise an organic alcohol, for example a C_{1-3}alcohol such as MeOH, EtOH, or n-PrOH, and most preferably comprises methanol. Optionally, said solvent may include dichloromethane.

In particularly preferred embodiments, said solvent is methanol. It has been found that the hydrochloride salt of the present invention has higher solubility in methanol than in other related organic solvents, and hence the use of methanol in the method of the present invention helps to avoid early precipitation of the salt.

Typically, said free base may be dissolved in said solvent at a concentration of 0.05-0.2, preferably 0.07-0.125, most preferably about 0.1, grams of free base per ml of solvent.

In preferred embodiments, said hydrogen chloride is added to said free base after the free base has been dissolved in said solvent. Optionally, however, said hydrogen chloride may be added to said free base before said free base has been dissolved or fully dissolved in said solvent.

In some embodiments, said hydrogen chloride comprises HCl gas dissolved in an organic solvent such as an organic alcohol, such as isopropanol, diethylether, ethanol, or methanol. Typically, in such embodiments, said hydrogen chloride has an HCl concentration of 3-8M, preferably 5-6M.

In other, preferred, embodiments, said hydrogen chloride comprises an aqueous solution of hydrochloric acid. Advantageously, said aqueous solution of hydrochloric acid is concentrated, having a concentration of at least 10M, preferably 11-12M.

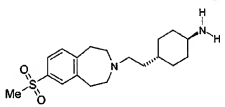
Advantageously, said hydrogen chloride may be added to said free base dropwise. Said hydrogen chloride may be added to said free base under reflux. Suitably, said hydrogen chloride may be added to said free base at a temperature of at least 60°C. Suitably, the reaction mixture of said free base and said hydrogen chloride is heated to or formed at at least 60°C, preferably under reflux.

Advantageously, said method may further include the step of hot-filtering the reaction mixture of free base and hydrogen chloride, in order to remove solid impurities. Preferably, said hot filtration may be carried out at a temperature of at least 60°C. In order to minimise the loss of any HCl salt which may have precipitated out of solution prior to said filtration, said filtrate and/or the filter may advantageously be washed down with hot methanol following said filtration, and the washings added to said reaction mixture.

Suitably, said method may further comprise the step of cooling said reaction mixture of free base and hydrogen chloride, preferably to room temperature or below, in order to allow said salt to crystallise. Advantageously, said reaction mixture may be seeded during cooling with small amounts of the hydrochloride salt of the compound of formula (I). Preferably, the rate of cooling is controlled so as to maximise the recoverability of salt from the reaction mixture.

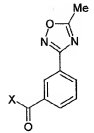
Advantageously, said salt may be recovered from said reaction mix by filtration following crystallisation thereof. Optionally, said salt may be recrystallised from ethanol and/or diethylether. This will serve to improve the purity of the salt.

Methods for the preparation of the free base of the compound of formula (I) are known in the art. Thus, for example, said free base may be prepared by reacting a compound of formula (II):



Formula (II)

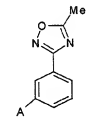
(a) with a compound of formula (III):



Formula (III)

wherein X is a halogen atom or the residue of an activated ester; or

(b) with a compound of formula (IV):

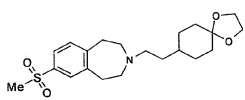


Formula (IV)

wherein A is Br, or I, or $-OSO_2CF_3$, in the presence of carbon monoxide and a catalyst such as *trans-bis*-triphenylphosphinepalladium(II)bromide.

Process (a) may be effected using conventional methods for the formation of an amide bond. When X is the residue of an activated ester this may be formed with e.g. a carbodiimide such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The reaction may be carried out in a solvent such as dichloromethane.

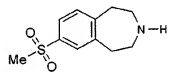
Compounds of formula (II) may be prepared by conversion of a compound of formula (V):



Formula (V)

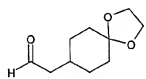
into a corresponding ketone, followed by reductive amination. This may be effected by methods well known in the art for (i) conversion of a ketal to a ketone in the presence of aqueous acid; followed by (ii) reductive amination of the ketone with NH_3 or ammonium acetate in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as methanol, ethanol or dichloroethane.

A compound of formula (V) may itself be prepared by reacting a compound of formula (VI):



Formula (VI)

with a compound of formula (VII):

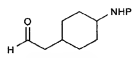


Formula (VII)

in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as ethanol or dichloroethane.

The individual *cis*- and *trans*- isomers of a compound of formula (II) may be prepared starting from *cis*- or *trans*- 4-amino-cyclohexaneacetic acid (T.P. Johnson, *et al.*, J. Med. Chem.,

1997, (20), 279-290) followed by functional group interchange and/or protection using methods well known in the art, to give the individual *cis*- or *trans*- isomers of a compound of formula (VIII):



Formula (VIII)

wherein P is a protecting group, for example trifluoroacetyl or *tert*-butoxycarbonyl. Subsequent reaction of a compound of formula (VIII) with a compound of formula (VI) in the presence of a reducing agent as described above followed by deprotection using standard methodology gives the individual isomers of a compound of formula (II).

Compounds of formula (III) and (IV) are known or may be prepared using standard procedures.

The salt of the present invention is expected to have utility as an antipsychotic agent, especially in the treatment of psychotic disorders including schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and delusional disorders. Furthermore, it could have utility as adjunct therapy in Parkinsons Disease, particularly with compounds such as L-DOPA and possibly dopaminergic agonists, to reduce the side effects experienced with these treatments on long term use (eg see Schwartz et al., Brain Res. Reviews, 1998, 26, 236-242). From the localisation of D3 receptors, it could also be envisaged that the salt could also have utility for the treatment of substance abuse where it has been suggested that D3 receptors are involved (eg see Levant, 1997, Pharmacol. Rev., 49, 231-252) . Examples of such substance abuse include alcohol, cocaine, heroin and nicotine abuse. Other conditions which may be treated by the salt of the present invention include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety, cognitive impairment including memory disorders such as Alzheimer's disease, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders and gastric motility disorders e.g. IBS.

In a further aspect therefore the present invention provides a method for the treatment or prophylaxis of psychotic disorders, substance abuse or addiction, dyskinetic disorders, depression, anxiety, cognitive impairment, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders, or gastric motility disorders, which comprises administering to a subject in need thereof an effective amount of the hydrochloride salt of the compound of formula (I), in particular the monohydrochloride salt thereof.

In one particularly preferred embodiment, said method is for the treatment of schizophrenia. In other particularly preferred embodiments, said method is for the treatment of substance abuse or addiction, including alcohol, heroin, cocaine or nicotine abuse or addiction.

In yet another aspect, the invention provides the use of the hydrochloride salt of the compound of formula (I) in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders, substance abuse or addiction, dyskinetic disorders, depression, anxiety, cognitive impairment, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders, or gastric motility disorders; in particular psychoses such as schizophrenia, and/or substance abuse or addiction such as alcohol, heroin, cocaine or nicotine abuse or addiction.

For the purposes of said method or treatment or prophylaxis, the hydrochloride salt of the present invention is usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect a pharmaceutical composition comprising the hydrochloride salt of the compound of formula (I) and one or more physiologically acceptable excipients and/or carriers.

The hydrochloride salt of the present invention may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions of the invention may be adapted accordingly.

The hydrochloride salt of the present invention when given orally can be formulated as a liquids or a solid, for example a syrup, suspension or emulsion, tablet, capsule or lozenge.

A liquid formulation will generally consist of a suspension or solution of the salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of said salt calculated as the free base.

The physiologically acceptable compositions of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of said hydrochloride salt calculated as the free base, the salt being administered 1 to 4 times per day. Suitably the salt will be administered for a period of continuous therapy, for example for a week or more.

Biological Test Methods

Binding experiments on cloned dopamine (e.g. D2, D3 and D4) receptors

The ability of the compounds to bind selectively to human D2/D3/D4 dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) of test compounds for displacement of [^{125}I]-Iodosulpride binding to human D2/D3 and [^{3}H]-YM-09151 to D4 dopamine receptors expressed in CHO cells were determined as follows. The cell lines were shown to be free from bacterial, fungal and mycoplasmal contaminants, and stocks of each were stored frozen in liquid nitrogen. Cultures were grown as monolayers or in suspension in standard cell culture media. Cells were recovered by scraping (from monolayers) or by

centrifugation (from suspension cultures), and were washed two or three times by suspension in phosphate buffered saline followed by collection by centrifugation. Cell pellets were stored frozen at -80°C. Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding. Preparation of CHO cell membranes: Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold Extraction buffer; 5mM EDTA, 50mM Trizma pre-set crystals (pH7.4@37°C), 1mM $MgCl_2$, 5mM KCl and 120mM NaCl. The suspension was homogenised using an Ultra-Turrax at full speed for 15 seconds. The homogenate was centrifuged at 18,000 r.p.m for 15 min at 4°C in a Sorvall RC5C centrifuge. Supernatant was discarded, and homogenate re-suspended in extraction buffer then centrifugation was repeated. The final pellet was resuspended in 50mM Trizma pre-set crystals (pH 7.4 @ 37°C) and stored in 1ml aliquot tubes at –80°C (D2 = 3.0E+08 cells, D3 = 7.0E+07 cells and D4 = 1.0E+08 cells). The protein content was determined using a BCA protocol and bovine serum albumin as a standard (Smith, P. K., et al., Measurement of protein using bicinchoninic acid. Anal. Biochem. **150**, 76-85 (1985)).

Binding experiments: Crude D2/D3 cell membranes were incubated with 0.03nM [^{125}I]-Iodosulpride (~2000 Ci/mmol; Amersham, U. K.) and D4 with 0.8nM [^{3}H]-YM-09151 (~85Ci/mmol; NEN, UK), and the test compound in a buffer containing 50mM Trizma pre-set crystals (pH 7.4 @ 37°C), 120mM NaCl, 5mM KCl, 2mM $CaCl_2$, 1mM $MgCl_2$, 0.3% (w/v) bovine serum albumin. The total volume is 0.2ml and incubated in a water bath at 37°C for 40 minutes. Following incubation, samples were filtered onto GF/B Unifilters using a Canberra Packard Filtermate, and washed four times with ice-cold 50mM Trizma pre-set crystals (pH 7.4 @ 37°C). The radioactivity on the filters was measured using a Canberra Packard Topcount Scintillation counter. Non-specific binding was defined with 10μM SKF-102161 (YM-09151). For competition curves, 10 serial log concentrations of competing cold drug were used (Dilution range: 10μM-10pM). Competition curves were analysed using Inflexion, an iterative curve fitting programme in Excel. Results were expressed as pKi values where pKi = -log10[Ki].

Measured pKi values of the monohydrochloride salt of the compound of formula (I) at the dopamine D_3 and D_2 receptors, and the D_3 vs. D_2 selectivity of this salt, are as follows. pKi results are estimated to be accurate to about ±0.2-0.3.

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D3 dopamine receptor	pKi = 8.4
D2 dopamine receptor	pKi = 6.4
D3 vs. D2 selectivity	100

Functional Activity at cloned dopamine receptors

The functional activity of compounds at human D2 and human D3 receptors (i.e. agonism or antagonism) may be determined using a Cytosensor Microphysiometer (McConnell HM et al Science 1992 257 1906-1912). In Microphysiometer experiments, cells (hD2_CHO or hD3_CHO) were seeded into 12mm Transwell inserts (Costar) at 300000 cells/cup in foetal calf serum (FCS)-containing medium. The cells were incubated for 6h at 37°C in 5%CO_2, before changing to FCS-free medium. After a further 16-18h, cups were loaded into the sensor chambers of the Cytosensor Microphysiometer (Molecular Devices) and the chambers perfused with running medium (bicarbonate-free Dulbecco's modified Eagles medium containing 2 mM glutamine and 44 mM NaCl) at a flow rate of 100 ul/min. Each pump cycle lasted 90s. The pump was on for the first 60s and the acidification rate determined between 68 and 88s, using the Cytosoft programme. Test compounds were diluted in running medium. In experiments to determine agonist activity, cells were exposed (4.5 min for hD2, 7.5 min for hD3) to increasing concentrations of putative agonist at half hour intervals. Seven concentrations of the putative agonist were used. Peak acidification rate to each putative agonist concentration was determined and concentration-response curves fitted using Robofit [Tilford, N.S., Bowen, W.P. & Baxter, G.S. Br. J. Pharmacol. (1995), Vol. 115, 160P]. In experiments to determine antagonist potency, cells were treated at 30 min intervals with five pulses of a submaximal concentration of quinpirole (100 nM for hD2 cells, 30 nM for hD3 cells), before exposure to the lowest concentration of putative antagonist. At the end of the next 30 min interval, cells were pulsed again with quinpirole (in the continued presence of the antagonist) before exposure to the next highest antagonist concentration. In all, five concentrations of antagonist were used in each experiment. Peak acidification rate to each agonist concentration was determined and concentration-inhibition curves fitted using Robofit.

The invention is further illustrated by the following non-limiting descriptions and examples :

Descriptions

P32781

Description 1

2,3,4,5-Tetrahydro-1*H*-3-benzazepine

1,2-Phenylenediacetonitrile (7.5g, 48 mmol) dissolved in ethanol (150ml) was added to Raney Ni (2g) which had been previously washed with ethanol (3x20ml). The mixture was then hydrogenated at 50°C at 50psi pressure with shaking for 24h. The reaction mixture was then cooled to room temperature and filtered through a pad of kieselguhr and washed through with ethanol (100ml). The filtrate was evaporated *in vacuo* to give a brown oil which was chromatographed on silica gel (100g), eluting with 2-10% methanol in CH_2Cl_2 to give the title compound as a brown oil (2.45g, 35%).

Mass spectrum (API^+) Found: 148 (MH^+). $C_{10}H_{13}N$ requires 147.

Description 2

3-Acetyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

A solution of acetic anhydride (6.37 g, 0.062 mol) in dichloromethane (50 ml) was added dropwise to a stirred solution of 2,3,4,5-tetrahydro-1*H*-3-benzazepine (8.35 g, 0.057 mol) (Description 1) and triethylamine (8.7 ml) in dichloromethane (50 ml) at 0 °C under argon. After stirring at room temperature for 18 h, water (80 ml) was added and the organic layer separated. The organic layer was washed with 0.5 M hydrochloric acid (50 ml), saturated sodium bicarbonate solution (50 ml), water (50 ml) and then dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave the title compound (10.24 g, 95 %) as a yellow oil which solidified on standing.

^1H NMR ($CDCl_3$) δ: 2.18 (3H, s), 2.85 - 3.00 (4H, m), 3.55 - 3.60 (2H, m), 3.72 - 3.80 (2H ,m), 7.10 - 7.20 (4H, m).

Mass Spectrum AP^+: Found 190 (MH^+). $C_{12}H_{15}NO$ requires 189.

Description 3

3-Acetyl-7-chlorosulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

A solution of 3-acetyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (4.0 g, 0.021 mol) (Description 2) in dichloromethane (25 ml) was added dropwise to a stirred solution of chlorosulphonic acid in dichloromethane (25 ml) at -70 °C under argon. After warming to room temperature, the reaction

was stirred for 18 h before being quenched in ice/water (200 ml). The resulting mixture was extracted with ethyl acetate (3 x 100 ml), dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give the title compound (2.74 g, 45 %) as a pale yellow solid.

^{1}H NMR: δ ($CDCl_3$): 2.21 (3H, s), 3.0 - 3.10 (4H, m), 3.60 - 3.70 (2H, m), 3.74 - 3.80 (2H, m), 7.35 - 7.40 (1H, m), 7.80 - 7.85 (2H, m).

Mass spectrum AP$^+$: Found 288 & 290 (MH^+). $C_{12}H_{14}NSO_2Cl$ requires 287 & 289.

Description 4

3-Acetyl-7-methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

To a stirred solution of sodium sulphite (1.60 g, 12. 6 mmol) and sodium hydrogen carbonate (1.14 g, 13.56 mmol) in water (25 ml) was added 3-acetyl-7-chlorosulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2.6 g, 9.04 mmol) (Description 3) in tetrahydrofuran (10 ml). The reaction mixture was then heated at 75 °C for 2 h, cooled to 30 °C and methyl iodide (2.8 ml, 45.20 mmol) added. After stirring at 50 °C for 24 h, the reaction mixture was cooled to room temperature and partitioned between water (50 ml) and ethyl acetate (100 ml). The aqueous layer was then separated and further extracted with ethyl acetate (2 x 80 ml). The combined organics were then dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound (1.77 g, 73 %) as a pale yellow solid.

^{1}H NMR ($CDCl_3$) 2.20 (3H, s), 2.99 - 3.05 (4H, m), 3.06 (3H, s), 3.61 - 3.64 (2H, m), 3.73 - 3.77 (2H, m), 7.32 - 7.37 (1H, m), 7.7 - 7.75 (2H, m).

Mass Spectrum AP$^+$: Found 268 (MH^+). $C_{13}H_{17}NSO_3$ requires 267.

Description 5

7-Methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

A solution of 3-acetyl-7-methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1.75 g, 6.55 mmol) (Description 4) in 5 M hydrochloric acid was heated at reflux for 18 h. The reaction mixture was then cooled to room temperature, basified to pH = 12 with potassium carbonate and the solvent evaporated *in vacuo*. The solid residue was then extracted with ethyl acetate (5 x 60

ml) and the combined organics dried (Na_2SO_4). The solvent was then evaporated *in vacuo* to give the title compound (450 mg, 32 %) as a pale yellow oil.

^1H NMR ($CDCl_3$) 1.88 (1H, br s), 2.95 - 3.13 (8H, m), 3.04 (3H, s), 7.25 - 7.30 (1H, d), 7.65 - 7.72 (2H, m).

Mass Spectrum AP^+: Found 226 (MH^+). $C_{11}H_{15}NSO_2$ requires 225.

Description 6

***trans*-2-(1-(4-(*N*- *tert*-Butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester**

A mixture of *trans*-(4-amino)cyclohexylactic acid hydrogen sulfate (T.P. Johnston *et al*; J. Med Chem., 1977, 20 (2), 279-290), (27.0g, 106mmol), conc. H_2SO_4 (3ml), and methanol (300ml) was stirred at reflux for 5h. Resulting solution was filtered and the filtrate evaporated *in vacuo* to give a brown oil (36g). A mixture of this material, triethylamine (36ml; 26.1g, 259 mmol), dichloromethane (600ml) and di-*t*-butyl dicarbonate (25.5g, 117mmol) was stirred at 20°C for 18h. Resulting solution was partitioned between saturated aqueous $NaHCO_3$ (500ml) and dichloromethane (3x200ml), and the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (24.6g, 86%) as a colourless solid.

^1H NMR ($CDCl_3$) δ: 1.08 (4H, m), 1.43 (9H, s), 1.76 (3H, m), 2.00 (2H, m), 2.20 (2H, d, J = 7 Hz), 3.37 (1H, m), 3.66 (3H, s), 4.39 (1H, br s).

Description 7

***trans*-2-(1-(4-(*N*-*tert*-Butyloxycarbonyl)amino)cyclohexyl)acetaldehyde**

To a stirred solution of *trans*-2-(1-(4-(*N*-*tert*-butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester (46.0g, 170 mmol) (Description 6) in dry toluene (920ml) at -78°C under argon was added a solution of di-isobutylaluminium hydride (1M; 285 ml; 285 mmol), dropwise over 0.5h. Resulting solution was stirred for a further 0.3h and quenched with a mixture of methanol (28ml) in toluene (50ml) and then poured into saturated aqueous potassium sodium tartrate (1.2L). The resultant mixture was extracted with ether (4x1L). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a waxy solid which was purified using silica gel, eluting with 10-50% ethyl acetate/hexane to give the title compound (21.77g, 53%) as a colourless solid.

^1H NMR ($CDCl_3$) δ: 1.12 (4H, m), 1.44 (9H, s), 1.78 (3H, m), 2.00 (2H, m), 2.33 (2H, dd, J = 7, 2 Hz), 3.37 (1H, m), 4.40 (1H, m), 9.75 (1H, m).

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Description 8

***trans*-3-(2-(1-(4-(N-tert-Butyloxycarbonyl)amino)cyclohexyl)ethyl-7-methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine**

A solution of 7-methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1.0 g, 4.67 mmol) (Description 5) and trans-(1-(4-*N-tert*-butyloxycarbonyl)amino)cyclohexylacetaldehyde (0.8 g, 3.34 mmol) (Description 7) in dichloroethane (20 ml) was stirred at room temperature for 5 min before sodium triacetoxyborohydride (0.95 g, 4.49 mmol) was added in a single portion. After stirring at room temperature for 48 h, the reaction mixture was partitioned between water (50 ml) and dichloromethane (100 ml). The aqueous layer was separate, re-extracted with dichloromethane (2 x 50 ml) and the combined organic layers dried (Na_2SO_4). The solvent was then removed *in vacuo* to give a pale yellow solid which was purified by column chromatography (silica gel; ethyl acetate : methanol; 9 : 1) to give the title compound (1.35 g, 90 %) as a colourless solid.

^{1}H NMR ($CDCl_3$): 0.99 - 1.14 (4H, m), 1.23 - 1.29 (1H, m), 1.41 - 1.46 (2H, m), 1.46 (9H, s), 1.73 - 1.79 (2H, m), 2.00 - 2.06 (2H, m), 2.50 (2H, t, J = 7.6 Hz), 2.62 - 2.65 (4H, m), 2.99 - 3.02 (4H, m), 3.05 (3H, s), 3.38 (1H, br s), 4.38 (1H, br s), 7.27 - 7.30 (1H, d), 7.67 - 7.74 (2H, m).

Mass spectrum: AP^+ Found: 351 ($[M\text{-}BOC]H^+$). $C_{24}H_{38}N_2SO_4$ requires 450.

Description 9

***trans*-3-(2-(1-(4-Amino)cyclohexyl)ethyl)-7-methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine**

A solution of trans-3-(2-(1-(4-*N-tert*-butyloxycarbonyl)amino)cyclohexyl)ethyl-7-methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (1.3 g, 2.89 mmol) (Description 6) in dichloromethane (24 ml) and trifluoroacetic acid (6 ml) were stirred at room temperature for 2 h. The reaction mixture was then concentrated *in vacuo* and the residue partitioned between water (60 ml) and ethyl acetate (20 ml). The aqueous layer was separated, extracted with ethyl acetate (30 ml) and then basified to pH = 14 with 40 % sodium hydroxide. The oily suspension was then extracted with ethyl acetate (3 x 60 ml) and the combined organic layers dried (Na_2SO_4). The solvent was evaporated *in vacuo* to give the title compound (1.01 g, 100 %) as an off-white solid.

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^{1}H NMR ($CDCl_3$) δ: 0.90 - 1.12 (4H, m), 1.15 - 1.22 (1H, m), 1.35 - 1.40 (2H, m), 1.72 - 1.78 (2H, m), 1.82 - 1.90 (2H, m), 2.45 - 2.52 (2H, m), 2.55 - 2.62 (5H, m), 2.98 - 3.02 (4H, m), 3.04 (3H, s), 7.27 (1H, d, J = 7.8 Hz), 7.56 (1H, s), 7.68 (1H, d).

Mass spectrum: AP^+ 351 (MH^+): $C_{19}H_{30}N_2SO_2$ requires 350.

Description 10

3-(3-Bromophenyl)-5-methyl-1,2,4-oxadiazole

Potassium *tert*-butoxide (7.33 g, 65.4 mmol) was added over 5 minutes to ice chilled, stirred methanol under argon. After a further 5 min hydroxylamine hydrochloride (4.9 g, 70.43 mmol) was added in one portion and the resultant mixture stirred at room temperature for 1 h. A solution of 3-bromobenzonitrile (7.93 g, 43.6 mmol) in methanol (120 ml) was added in one portion and the mixture heated at reflux for 4 h, cooled filtered, and the filtrate evaporated *in vacuo*. The residue was refluxed in acetic anhydride (60 ml) for 3 h, cooled to room temperature and poured into ice-water (300 ml). The precipitate was filtered, washed with water, dried *in vacuo* and chromatographed on silica eluting with 0 - 10% ethyl acetate - hexane gradient. Fractions containing desired product were pooled and evaporated *in vacuo* and the residue recrystallised from hexane to afford the title compound as colourless crystals (5.2 g, 50 %).

Mass spectrum: (API^+) Found: 239 (MH^+). $C_9H_7{}^{79}BrN_2O$ requires 238

^{1}H NMR ($CDCl_3$) δ: 2.66 (3H, s), 7.36 (1H, t, J = 8 Hz), 7.63 (1H, m), 8.05 (1H, m), 8.23 (1H, m).

Description 11

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-benzoic acid

A mixture of 3-(3-bromophenyl)-5-methyl-1,2,4-oxadiazole (2.68 g, 11.3 mmol) (Description 10), tributylamine (3.05 ml, 12.5 mmol) and *trans*-dibromobis(triphenylphosphine)palladium (II) (0.13 g, 0.16 mmol) in methanol (5 ml) was carbonylated at 30 psi and 100 °C for 18 h. The mixture was cooled to room temperature, diluted with ethyl acetate (100 ml) and washed sequentially with saturated sodium hydrogen carbonate (2 x 300 ml), brine (100 ml), 0.5 N hydrochloric acid (200 ml), brine (100 ml), then dried Na_2SO_4) and evaporated *in vacuo* to afford a yellow oil (2.49 g). A 2 g sample of this oil was dissolved in aqueous methanol (5:3, 80 ml), sodium hydroxide (0.36 g) added and the mixture stirred at room temperature for 20 h. The mixture was evaporated *in vacuo* and the residue partitioned between ethyl acetate (100 ml) and

water (100 ml). The aqueous layer was acidified with 2N HCl and the resultant precipitate filtered, washed with water and dried *in vacuo* to afford the title compound as a colourless solid (0.78 g, 42 %).

Mass spectrum: (API^+) Found: 205 (MH^+). $C_{10}H_8N_2O_3$ requires 204.

^1H NMR ($CDCl_3$) δ: 2.70 (3H, s), 7.71 (1H, m), 8.14 (1H, dd, J = 7,1 Hz), 8.23 (1H, dd, J = 7, 1 Hz), 8.54 (1H, m), 13.35 (1H, br s).

Description 12

***trans*-3-(2-(1-(4-(3-(3-(5-Methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine**

A mixture of *trans*-3-(2-(1-(4-amino)cyclohexyl)ethyl)-7-methylsulphonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (100 mg, 0.29 mmol) (Description 9), 3-(3-(5-methyl)-1,2,4-oxadiazolyl)-benzoic acid (69 mg, 0.34 mmol) (Description 11), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (59 mg, 0.31 mmol) and 1-hydroxybenzotriazole (cat. amt.) in dichloromethane (10 ml) was shaken at room temperature for 18 h. A saturated solution of sodium bicarbonate (4 ml) was then added and the mixture shaken for 0.25 h. The organic layer was then applied directly to a silica column eluted with a gradient of 30 - 100% ethyl acetate in hexane and then 0 - 10% methanol in ethyl acetate to give the title compound (103 mg, 69 %) as a colourless solid.

^1H NMR δ ($CDCl_3$): 1.08 - 1.30 (5H, m), 1.40 - 1.46 (2H, m), 1.80 - 1.85 (2H, m), 2.08 - 2.15 (2H, m), 2.52 (2H, t, J = 7.8), 2.60 - 2.65 (4H, m), 2.68 (3H, s), 2.98 - 3.02 (4H, m), 3.05 (3H, s), 3.90 - 4.00 (1H, m), 6.01 (1H, d, J = 8.0 Hz), 7.28 (1H, d, J = 7.28 Hz), 7.57 (1H, t, J = 7.8 Hz), 7.65 - 7.70 (2H, m), 8.0 (1H, d), 8.19 (1H, d, J = 7.7 Hz), 8.32 (1H, s).

Mass spectrum: API^+ 537 (MH^+): $C_{29}H_{36}N_4SO_4$ requires 536.

Examples

Synthesis of *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride.

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Example 1

Trans-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) (2g, 0.0037mol.) was suspended in methanol (20ml) and heated to reflux. To this was added a solution of HCl in IPA (1.36ml of a 5.5M solution, 0.0075mol) in one portion. The solid immediately went into solution. The solution was stirred for 30 minutes to allow the salt to crystallise then cooled slowly to room temperature and stirred overnight. The resulting white solid was filtered off, washed with ice cold methanol (8ml) then dried *in vacuo* at 60°C overnight to give *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (1.97g, 92.3%).

Example 2

Trans-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) (27g, 0.0503mol.) was suspended in methanol (270ml) and heated to reflux. To this suspension was added concentrated hydrochloric acid (5.4ml, 0.0612mol) over about 5 minutes. The solid went into solution during this addition. The solution was filtered and then cooled slowly to room temperature over 2 hours (the product crystallised at 55°C). The reaction was stirred at room temperature overnight and the product filtered off, washed with ice cold methanol (50ml) and dried *in vacuo* at 60°C for 6 hours to give *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (25.74g, 89.3%).

Example 3

Trans-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) (5g, 0.0093mol.) was suspended in methanol (100ml) and heated to reflux. To this was added concentrated hydrochloric acid (0.97ml, 0.0116mol) over 5 minutes. The solid went into solution during this addition. The reaction solution was filtered and the filter paper washed with hot methanol (10ml). 60ml of solvent was distilled from the reaction and the reaction was then cooled to room temperature (product crystallised at 54.5°C) and stirred for 4 hours. The product was filtered off, washed with ice cold methanol (10ml) and dried *in vacuo* at 60°C overnight to give *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (4.73g, 88.7%).

Example 4

Trans-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) (5Og, 0.093mol.) was suspended in methanol (1000ml) and heated to reflux. To this was added concentrated hydrochloric acid (9.7ml, 0.0116mol) over 35 minutes. The solid went into solution during this addition. The acid was washed in with a further portion of methanol (250ml). The reaction solution was filtered and the filter paper washed with hot methanol (250ml). The reaction was then concentrated to a total reaction volume of 880ml. The reaction was cooled to 38.6°C, seeded with SB-414796-A (0.05g) (product crystallised after seeding), then cooled to room temperature and stirred for 3 hours 45 minutes. The product was filtered off, washed with ice cold methanol (100ml) and dried *in vacuo* at 60°C overnight to give *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (44.72g, 84%).

Example 5

Trans-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) was dissolved in dichloromethane. To this solution was added 1.1eq HCl in diethylether. The resulting HCl salt *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride was recrystallised from EtOH/Et_2O to give a white solid (2.60g yield).

Example 6

Trans-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) was dissolved in dichloromethane/methanol at room temperature. To this was added 1.0M HCl and the reaction was stirred for 10 mins. Solvents were then evaporated in vacuo to give a waxy white solid. Hot i-PrOH was added and the resulting mixture was cooled to 0°C and filtered to give *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride. The sample was dried at 40°C under vacuum for 18 hours, yielding a lumpy white solid. For recrystallisation from EtOH, the solid was added to 1.5L of ethanol at gentle reflux over 0.3 hours. The resulting mixture was heated at reflux with overhead stirring for 0.5 hours, after which the solution went clear and was filtered hot into a 2L

conical flask. Remaining solid was boiled up with further ethanol (100ml) and the resulting solution was used to wash through the filter. Precipitation of fine solid commenced on cooling. The flask was cooled to 4°C, then the resulting solid was collected by filtration (8.3g, 80%). The solid was dried in vacuo at 65°C.

Example 7

Trans-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) was dissolved in dichloromethane/methanol. 1.0M HCl slowly under stirring, and the resulting mix was stirred at room temperature for 15 mins. Solvents were then evaporated in vacuo to yield a waxy solid (*trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride). The salt was purified by dissolving in refluxing EtOH (2.9L) and then cooling to 4°C overnight. The product was isolated by filtration and dried for 8 hours at 60°C in vacuo to give for 6 hours to give purified *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride (18.4g, 88%).

Example 8

A solution of HCl gas in ether was added to a solution of *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) in dichloromethane/methanol. The mixture was stirred for 30 mins and then solvents were evaporated off to yield a solid product. The solid was recrystallised from boiling EtOH to yield *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride.

Example 9

Trans-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Description 12) was dissolved in boiling n-propanol. 2M hydrogen chloride gas dissolved in isopropyl alcohol was added and the mixture was hot-filtered to remove impurities. The mixture was cooled to allow precipitation of *trans*-3-(2-(1-(4-(3-(3-(5-methyl)-1,2,4-oxadiazolyl)benzoyl)amino)cyclohexyl)ethyl)-7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride which could then be isolated by filtration.

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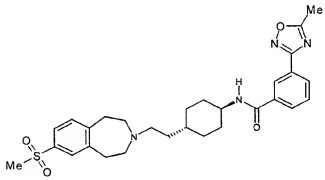
Claims

1. A hydrochloride (HCl) salt of the compound of formula (I) :



Formula (I)

2. A salt as claimed in claim 1, which salt is a monohydrochloride salt.

3. A salt as claimed in claim 2 or claim 3, in anhydrous form substantially free from hydrated forms of said salt.

4. A salt as claimed in any preceding claim, substantially free from the free base form of the compound of formula (I) and/or other salts thereof.

5. A salt as claimed in any preceding claim, in isolated form.

6. A salt as claimed in any preceding claim for use as an active therapeutic substance.

7. A salt as claimed in any preceding claim, for use in the treatment or prophylaxis of psychotic disorders, substance abuse or addiction, dyskinetic disorders, depression, anxiety, cognitive impairment, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders, or gastric motility disorders.

8. A pharmaceutical preparation comprising a salt as claimed in any preceding claim, and one or more physiologically acceptable excipients or carriers.

9. Use of a salt as claimed in any of claims 1-7 in the preparation of a medicament for use in the treatment or prophylaxis of psychotic disorders, substance abuse or addiction, dyskinetic disorders, depression, anxiety, cognitive impairment, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders, or gastric motility disorders.

10. Use as claimed in claim 9, wherein said medicament is for use in the treatment of psychotic disorders including schizophrenia, or substance addiction or abuse, including alcohol, cocaine, heroin or nicotine addiction or abuse.

11. A method for the treatment or prophylaxis of psychotic disorders, substance abuse or addiction, dyskinetic disorders, depression, anxiety, cognitive impairment, eating disorders, sexual dysfunction, sleep disorders, emesis, movement disorders, obsessive-compulsive disorders, amnesia, aggression, autism, vertigo, dementia, circadian rhythm disorders, or gastric motility disorders, which comprises administering to a patient in need thereof an effective amount of a salt as claimed in any of claims 1-7.

12. A method for preparing a hydrochloride salt as claimed in any of claims 1-7, comprising the steps of:
dissolving or suspending in a solvent a compound of formula (I) in free base form; and
mixing said free base with hydrogen chloride to allow formation of said salt.

13. A method as claimed in claim 12 for preparing the hydrochloride salt, starting from the free base.

14. A method as claimed in claim 12 or 13, further comprising the step of causing or allowing said salt to crystallise and isolating said crystallised salt.

15. A method as claimed in claim 12, 13 or 14, wherein said solvent is methanol.

16. A method as claimed in claim 15, wherein said free base is dissolved in methanol at a concentration of 0.05-0.2, preferably 0.07-0.125, most preferably about 0.1, grams of compound per ml of methanol.

17. A method as claimed in any of claims 12-16, wherein said hydrogen chloride comprises HCl gas dissolved in an organic solvent such as an organic alcohol, such as isopropanol, diethylether, ethanol, or methanol, or concentrated aqueous hydrochloric acid.

18. A method as claimed in any of claims 12-17, wherein the reaction mixture of said free base and said hydrogen chloride is heated to or formed at at least 60°C, preferably under reflux.

19. A method as claimed in claim 18, further comprising the step of hot-filtering said reaction mixture to remove solid impurities.

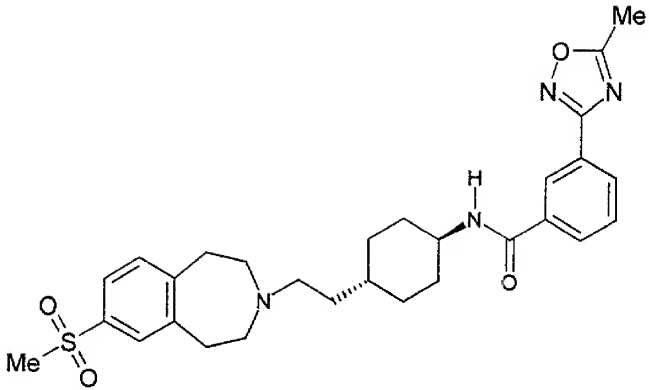
20. A method as claimed in claim 18 or claim 19, further comprising the step of cooling said reaction mixture, preferably to room temperature or below, to allow crystallisation of said salt.

21. A method as claimed in any of claims 12-20, further comprising the step of seeding the reaction mixture of said free base and said hydrogen chloride with small amounts of a hydrochloride salt of the compound of formula (I).

22. A method as claimed in any of claims 12-21, wherein said salt is isolated by filtration and is optionally recrystallised.

23. A method substantially as hereinbefore described with reference to the examples.

24. A salt obtainable by the method of any of claims 12-23.



(I)